

## Effects of nonstrangulated small bowel obstruction on intestinal histology, insulin-like growth factor-I level, antioxidants, and lipid peroxidation in rats

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Intestinal obstruction is a common disorder in surgical practice with significant morbidity and mortality. The early diagnosis of small bowel obstruction (SBO) is critical in preventing complications and avoiding excess morbidity and mortality that may result from delayed operation. However, controversy still exists regarding early operative versus conservative initial treatment. Clinical judgment and laboratory data are often unreliable in distinguishing between simple versus complicated SBO. Lipid peroxidation and protein oxidation caused by free oxygen radicals result in structural and functional cell damage.<sup>1</sup> Under normal conditions, free radicals generated during cell metabolism are rapidly scavenged by endogenous antioxidant enzymes. The most important indicators of ischemia-reperfusion injury are the increase in lipid peroxidation and change in the antioxidant enzyme activities.<sup>2</sup> The insulin-like growth factor (IGF-I) is present and synthesized locally within the gut. This peptide exerts a variety of anabolic and functional effect on tissues. Serum levels of IGF-I increase with age and pubertal development. Ischemic injury to the gut is known in strangulated intestinal ischemia model. Ischemia parameters in proximal and distal intestinal segments, however, have not been assessed earlier in a nonstrangulated intestinal obstruction model. The aim of this study was to investigate the changes of the intestinal wall morphometry, malondialdehyde (MDA), superoxide dismutases (SOD), catalase (CAT) levels, and IGF-1 levels in the presence of delayed operation for nonstrangulated SBO.

This study was carried out on 10 adult female albino Wistar rats weighing between 220-250 g. The animals were acquired from the university vivarium sources and were housed in individual cages in a temperature and light-dark cycle controlled environment with free access to food and water. All animals received humane care, in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985).

Surgical procedures were performed using a sterile technique under 5% ketamine hydrochloride anesthesia (50 mg/kg, intramuscular). A midline abdominal incision was performed to get access the ileum after skin shaving and preparation with 10% povidone-iodine solution. Small bowel obstruction was created in the SBO group by ligating an ileal loop, which located 10 cm proximal from ileocecal valve with 3/0 silk. After 48 hours, the rats were sacrificed with an overdose of pentobarbital sodium and ileal resection including 1 cm of proximal and distal loop to the obstruction was performed. The resection materials were divided longitudinally into 2 halves for histopathologic evaluation and biochemical assays. Specimens for histopathologic evaluation were individually immersed in neutral formalin fixative and dehydrated with a graded series of ethyl alcohol and embedded in paraffin. Sections (5  $\mu$ m) were cut and stained with hematoxylin and eosin. The length of intestinal villi were measured in micrometers ( $\mu$ m) and Chiu score (0-5) was evaluated for both proximal and distal of obstructed ileal sections.<sup>3</sup>

Specimens for biochemical assays were placed in glass bottles with rubber caps, labeled and stored at the  $-78^{\circ}\text{C}$  until assay. Briefly, the frozen sample of rat intestine was weighed and homogenized (Ultra Turrax T25, Germany) (1:10, w/v) in 100 mmol/L phosphate buffer (pH 7.4) containing 0.05% sodium azide in an ice bath. The homogenate was sonicated (Bandelin, Germany) for 30 seconds and centrifuged (5000 g for 10 minutes at  $4^{\circ}\text{C}$ ). The supernatant was frozen at  $-80^{\circ}\text{C}$  in aliquots until used for biochemical assays. The protein content of the supernatant was determined using the Lowry method.<sup>4</sup> The concentration of IGF-1 in the supernatant was determined using immunoradiometric assay kit for IGF-1 (Immunotech, Marseille, France) according to the manufacturer's specifications.

Malondialdehyde was estimated by the double heating method of Draper and Hadley.<sup>5</sup> The concentration of MDA was calculated by the absorbance coefficient of the MDA-TBA complex (absorbance coefficient  $\epsilon = 1.56 \times 10^5 \text{ cm}^{-1} \cdot \text{M}^{-1}$ ). Superoxide dismutase activity was measured according to the method of Spitz and Oberley.<sup>6</sup> Results are expressed as units per milligram of protein (U/mg protein). Catalase activity was measured according to the method of Aebi.<sup>7</sup> Results are expressed as catalytic activity per milligram protein (cat/mg protein). All statistical analysis was performed using the Statistical Package for Social Sciences version 9 software (SPSS Inc., Chicago, IL, USA). Data were expressed as mean  $\pm$  standard deviation. Differences among groups were analyzed by one-way analysis of variance (ANOVA)

followed by the Wilcoxon test as a post-hoc for multiple comparisons. A probability value less than 0.05 was considered significant ( $p < 0.05$ ).

We observed significant distension of the bowel proximal to the site of the obstruction. However, at the distal site of the obstruction there was no significant difference in the diameter of the small intestine. The IGF-I, MDA, SOD, CAT levels, villus lengths, and Chiu scores were shown at **Table 1**. There was a significant difference between IGF-I levels in the proximal site and the distal site of the obstruction ( $p < 0.05$ ). The MDA levels were significantly different at the proximal and the distal site of the obstruction ( $p < 0.05$ ). There was no significant difference between SOD levels in the proximal site and the distal site of the obstruction ( $p > 0.05$ ). There was no significant difference between CAT levels in the proximal site and the distal site of the obstruction ( $p > 0.05$ ). Villus length of the proximal site of the obstruction was  $441.75 \pm 51.68 \mu\text{m}$ . Villus length of the distal site of the obstruction was  $583.50 \pm 80.08 \mu\text{m}$ . There was a significant difference between villus length in the proximal site and the distal site of the obstruction ( $p < 0.05$ ). The Chiu score of the proximal site of the obstruction was  $2.7 \pm 0.72$ . The Chiu score of the distal site of the obstruction was  $0.3 \pm 0.46$ . There was a significant difference between Chiu scores in the proximal site and the distal site of the obstruction ( $p < 0.05$ ).

The optimal treatment of patients with SBO should be predicated upon answering the questions in each patient, is immediate operation necessary, or is a period of observation appropriate? Mechanical SBO is accompanied first by the development of mild proximal intestinal distension that results from the accumulation of normal gastrointestinal secretions and gas above the obstructed segment. Initially, this distension physiologically stimulates peristalsis above and below the point of obstruction. The intestinal smooth muscle response to the obstruction is remarkable and is represented by a smooth muscle mass increase due to hypertrophy and hyperplasia. Oxidative stress occurs in physiological conditions after an overproduction of reactive oxygen species (ROS) or a decrease of antioxidant substances or enzymes.<sup>2,8</sup> The measurement of MDA served as an indicator of free radical mediated tissue damage, which is responsible for intestinal ischemic injury. Our study showed that MDA level of the proximal site of the obstruction was higher than distal site. The IGF-I level of proximal site of obstruction was higher than the distal site in our study. Growth factors are

**Table 1** – The IGF-I, MDA, SOD, CAT levels, villus lengths, and Chiu scores of proximal and distal small bowel segments are shown ( $*p < 0.05$ ). Values are given as mean  $\pm$  standard deviation.

Levels	Proximal segment	Distal segment
IGF-I (ng/mg protein)*	116.41 $\pm$ 7.37	92.58 $\pm$ 3.42
MDA (nmol/mg protein)*	30.55 $\pm$ 4.84	12.39 $\pm$ 1.11
SOD (U/mg protein)	11.05 $\pm$ 0.35	10.44 $\pm$ 0.3
CAT (Cat/mg protein)	0.716 $\pm$ 0.009	0.674 $\pm$ 0.01
Villus length ( $\mu\text{m}$ )*	441.75 $\pm$ 51.68	583.5 $\pm$ 80
Chiu score*	2.7 $\pm$ 0.72	0.3 $\pm$ 0.46

IGF-I - insulin-like growth factor, MDA - malondialdehyde,  
SOD - superoxide dismutases, CAT - catalase

also considered major factors in intestinal adaptation. Stimulation of the intestinal mucosa proliferation by growth factors may be responsible for their protective effect against injury. Both SOD and CAT levels were not different between proximal and distal sites of the obstruction. It might be due to excessive consumption of antioxidant enzymes by free radicals or due to shorter duration of the intestinal obstruction for production of these enzymes. It also indicates an intact antioxidant defense system without any defect hence, relating the tissue damage to the increased ROS production. At the proximal site of the obstruction, intestinal villus length was shorter than the distal in our study. It has been reported that villi were injured due to circulatory insufficiency in the early stages in mechanical intestinal obstruction, and that intestinal segment dilated due to obstruction becomes effected more by ischemia. Chiu scores of the proximal site of the obstruction were higher than distal site. Although, we did not measure intraluminal pressure in the proximal segment; decreased villus length might be due to increased intraluminal pressure. Although smooth muscle hypertrophy was not seen in the present study, longer periods of partial obstruction might result in muscular hypertrophy in the proximal segment.

In conclusion, proximal bowel injury due to free radicals is observed in the rat model of nonstrangulated SBO. Decreased villus length might be due to increased intraluminal pressure and insufficient mucosal blood flow as a consequence of it. Our study also predicts that, 48 hours of obstruction is adequate for biochemical and histological changes, which indicate an injury to the proximal segment of nonstrangulated SBO.

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## Ultrastructural investigation of the protective role of folic acid and vitamin E against toxic effects of valproic acid on maternal liver tissue during period of gestation

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Valproic acid (VPA) is an anticonvulsant widely used in treatment of various forms of epilepsy. Valproic acid therapy, however, has been associated with a rare, but severe and sometimes fatal hepatotoxicity. As early as 1979 and 1980, the first case reports of VPA induced hepatic failure were published. The increased clinical use of VPA has been accompanied by reports of hepatic dysfunction and renal tubular defects.<sup>1</sup>

The mechanisms underlying the toxic effects of VPA has not been clearly established, and it has been suggested that it interferes in the folate cycle and therefore, with the methionine/methylation, possibly through a metabolic blocking of some biomarker that is a key of the cycle, such as for example S-

adenosylmethionine and folic acid (FA). Decrease in FA is accompanied by increased generation of free radicals and decrease in antioxidant defense of body. Chronic treatment with VPA has been shown to decrease the levels of antioxidants such as vitamin E (Vit E) and glutathione peroxidase further suggesting the role of oxidative stress.<sup>2</sup>

Published reports on valproate-induced hepatotoxicity provide sufficient information on the pathological changes induced in these cells. However, only one of them has described these changes on maternal liver tissue during gestation and none of them studied VPA with FA and Vit E during gestation.<sup>3</sup> The purpose of this study was to evaluate the protective role of FA and Vit E against the toxic effects of VPA on maternal liver tissue during period of gestation.

This study was performed, after the approval of Dicle University Ethic Council, on 28 adult female Wistar-Albino rats weighing 200-250 g obtained from Dicle University Health Sciences Investigation and Application Center (DUHSIAC). The rats were kept in a room with a temperature between 21-23°C, continuously ventilated by fans, and with 12 hours dark and 12 hours light. The rats were feed by ad-libitum standard pellet rat food and daily fresh tape water was given. The female rats were then separated for 20 days from the male rats then again coupled with male rats. The female rats were then examined using cervical plug. The female rats with positive cervical plug were accepted as pregnant and randomly assigned into 4 groups as following:

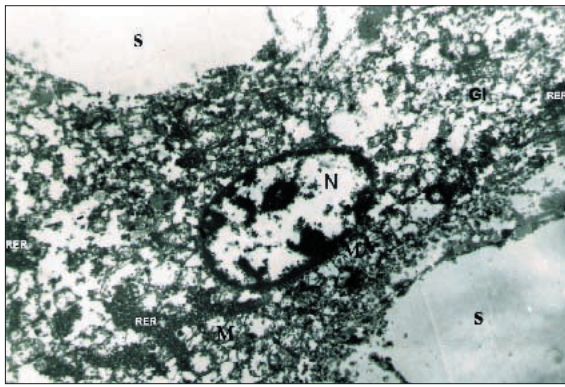
**Control group.** This group was injected with 0.3 ml subcutan physiologic saline solution to loose the subcutaneous zone on the back of the leg at 8th, 9th and 10th days of pregnancy.

**Valproic acid (VPA) group.** This group was injected with 400 mg/kg dosage of subcutan VPA (Na-valproate Sigma P 4543) after dilution, watered with saline solution to loose the subcutaneous zone on the back of the leg at 8th, 9th and 10th days of pregnancy.

**Valproic acid plus folic acid (VPA+FA) group.** The rats were injected with 400 mg/kg dosage of subcutan VPA (Na-valproate Sigma P 4543) after dilution, watered with saline solution to loose the subcutaneous zone on the back of the leg at 8th, 9th and 10th days of pregnancy. Also during pregnancy, 400 /lg FA (Pteryoglutamic acid vit M, Sigma F 8798) was ordinarily added to the drinking water of the female rats.

**Valproic Acid + Vitamin E (VPA+Vit E) group.** One hour before the VPA injection, 250 mg/kg of Vit E ( $\alpha$ -Tocopherol, Sigma T-3251) was given by





**Figure 1** - Electron micrograph of liver rat from the VPA+FA group. Nucleus (N), sinusoid (S), rough endoplasmic reticulum (RER) and glycogen deposits (GI) appear intact. Some mitochondria (M) with indistinct cristae are present. Lead citrate-uranyl acetate,  $\times 3000$ .

dilution with olive oil via nasogastric intubation. Then the rats were injected with 400 mg/kg dosage of subcutan VPA (Na-valproate Sigma P 4543) after dilution, watered with saline solution to loose the subcutaneous zone on back leg at 8 th, 9 th and 10th days of pregnancy.

On the 20th day of gestation anesthesia with 25 mg/kg ketamine was administered on the right leg interior side, subcutaneously and female rats were sacrificed. The liver was removed from each group and small cubes of liver were fixed in 2.5% phosphate buffered glutaraldehyde. After pontification with 1% osmic acid, they were dehydrated with acetone and semithin sections of tissue samples from blocked with araldite were stained with toluidine blue. Then the thin sections were stained with uranyl nitrate-lead acetate and examined under jeol 1010 transmission electron microscopy and microphotographs were received.

In the slides of liver sections of the control group, the appearance of the mitochondria, nucleus, sinusoids, and rough endoplasmic reticulum were histologically normal. In the VPA group, rough endoplasmic reticulum was normal and accumulation of glycogen and large vacuoles was determined. Occasional lipid droplets and electron dense mitochondria were seen. In the VPA+Vit E group, cisterna of the rough endoplasmic reticulum was short and few, mitochondria were not electron dense like VPA group, but some crystals were determined. Additionally, occasional glycogen accumulation and vacuoles were observed. In the VPA+FA group, rough endoplasmic reticulum, nucleus, sinusoids were seen and dense of glycogen were normal in some mitochondria crystals. (**Figure 1**)

Emmanouil-Nikoloussi et al<sup>3</sup> first assess the effects of VPA on both fetal and maternal organs during the period of gestation and in contrast to our study, they reported that there were no detectable morphological changes in the fetal or maternal organs by routine histology, immunocytochemistry or electron microscopy. Graf et al<sup>4</sup> administrated VPA for 3 days like our study and studied adult female mice and reported that occasionally, mitochondrial swelling, an increased number of lipid droplets and autophagic vacuoles could be observed in some hepatocytes as determined our study. Jimenez-Rodriguezvila et al<sup>5</sup> reported periportal steatosis in female rats after 4 weeks of treatment with only 120 mg/kg VPA per day administered via their drinking water. In contrast to these reports, Loscher et al<sup>6</sup> found no evidence of pathological changes in the liver of female rats after 6 weeks of treatment with 200 mg/kg VPA.

Jezequel et al<sup>7</sup> has reported that a single dose of VPA (200 or 600 mg/kg intraperitoneally administered) in rats produced ultrastructural changes in hepatocytes, including formation of autophagic vacuoles, engulfing mitochondria and occasionally peroxisome, after 3 and 5 hours. However, bile canaliculi and junctional complexes remained unaltered throughout exposure (12 hour). A modest accumulation of lipoprotein particles was evident at 5 hour in the Golgi cisternae. In another study, prolonged administration of VPA for 7 days (500 mg/kg) showed enlarged mitochondria.<sup>1</sup>

Our results confirmed previous reports on histopathologic changes induced by VPA in rats. Although the findings herein are consistent with those previously reported, the route of administration and the doses given were substantially different from those of their studies.

Buchi et al<sup>8</sup> studied the protective effect of Vit E against VPA injury in isolated rat hepatocytes and reported that VPA toxicity can be prevented by simultaneous administration of free-radical scavengers like Vit E. The decrease in toxicity could simply be a consequence of Vit E stabilizing the hepatocyte membrane, allowing for less lactate dehydrogenase to be released into the surrounding media and thus, decreasing the lactate dehydrogenase index. In this study, we determined that in VPA+Vit E group mitochondria were not electron dense like VPA group.

Valproic acid reduces blood folate levels and causes folate deficiency in both humans and laboratory animals. Chronic treatment of rats with VPA caused a decrease in liver folate concentration with concomitant increases in brain and plasma folate concentrations. Ubeda et al<sup>2</sup> has reported that VPA alters methionine metabolism by inhibiting enzyme

methionine adenosyltransferase activity in vivo and an alteration of methionine metabolism could be the single mechanism underlying the pathophysiology of the different potentially toxic effects of VPA, such as, hepatotoxicity, teratogenicity and the antifolate effect. However, the relationship of these metabolic changes to hepatic injury and teratogenicity remains to be elucidated.<sup>2</sup> Parallel to this information, we also determined that the ultrastructural changes in the liver of the VPA+FA group were lesser compared with the VPA group.

In conclusion, both Vit E and FA have a protective effect against the toxic effects of VPA on maternal liver tissue during period of gestation; however FA has a better protective role than Vit E.

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## Are the laws or applications insufficient to prevent children from the hazards of corrosive materials?

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Accidents caused by corrosive materials may result in death; however, these accidents are preventable. We collected the data by interviewing with the parents or relatives of 111 children who were taken to our hospital in January 2002-June 2004, suffering from the injuries caused by corrosive materials due to negligence and carelessness of their parents, and by examining the patient files and judicial records. The Statistical Package for Social Sciences version 10 program was used for the statistical evaluation.

One of the hazards that children frequently face at home is alkali and acid poisoning. The ingestion of liquid or solid corrosive materials results in severe esophageal or gastric damages, which lead to perforation or obstruction. In our country, corrosive materials and other cleaning products are not only sold in their original labeled bottles in supermarkets but, also in any container in the shops selling cleaning products.

Article 11 of the Food Products Statute provides for that cleaning products should be sold in their original bottles and Article 654 of the same Statute lies down that the main solutions of bleachers are merely permitted to be sold in their originally labeled bottles and that all bottles should have an instruction which illustrates how to use the product.

Articles 455, 456, 459, 460, 476/2, 530 of the Turkish Penal Code are conceived to be applicable to corrosive material injuries.

Articles 455 and 459 of the Turkish Penal Code are the most applicable articles in case of a corrosive material injury.

Article 455 of the Turkish Penal Code, which deals with causing death through imprudence, provides for that a person held responsible for the death of another

person through imprudence or negligence is sentenced to a fine and 2-5 years imprisonment.

Article 530 of the Turkish Penal Code provides for that the physicians are responsible for informing the judicial authorities after the urgent medical intervention in case of an incidence resulting from a crime, and they will, otherwise, be sentenced to fine.

Article 22 titled Negligence, Paragraph 6 of the new Turkish Penal Code no. 5237 enacted on 1 June 2005 provides that "if a negligent act results in the grievance of the offender, rendering the implementation of punishment unnecessary in terms of personal and familial situation, the punishment shall not be executed." Hence, the pain of a mother who has lost her child aggravates and the family is aggrieved. A judge who takes the account of this paragraph may not impose punishment on the offender.

The objective of this study is to find out the causes and frequency of corrosive accidents, research their medical and legal aspects and discuss the legal and practical measures to be taken in order the prevent accidents resulting from the negligence of parents. Among the children forming the sampling group of the research, 6 children (5.4%) were 0-6 month old, 39 (35.2%) were 1-2 years old, 30 (27%) were 3-4 years old, 19 (17.1%) were 5-6 years old, and 17 (15.3%) were 7 years old and over. Forty-one of the children (36.9%) were female whereas 70 of them (63.1%) were male. The youngest of the mothers were 21 and the eldest was 43 years old. The average age of the mothers was found  $28.57 \pm 5.46$  whereas that of fathers was  $32.32 \pm 5.87$ . Twenty-four families (21.6%) had one child, 61 families (55%) had 2 children, 19 families (17.1%) had 3 children and 7 families (6.3%) had more than 3 children. Four of the mothers (3.6%) and 3 of the fathers (2.7%) had no educational background. Seventy mothers (63.1%) and 40 fathers (36%) were primary school graduates, 33 mothers (29.7%) and 61 fathers (55%) were secondary school graduates and 4 mothers (3.6%) and 7 fathers were (6.3%) university graduates. None of the mothers had an occupation, which brings income and 13 of the fathers (11.7%) were unemployed. Fifty-six fathers (50.4%) had an occupation and had a permanent income, 22 fathers (19.8%) were operating their own business and 20 fathers (18%) were daily wage employees. Seventy-one incidents (64%) occurred in kitchen, 20 incidents (18%) in other parts of the house (rooms, living room, hall, and so forth), 11 incidents (9.9%) in bathroom and 9 incidents (8.1%) outside the house (garden, garage). Twenty-three incidents (20.7%) occurred during housecleaning, 8 incidents (7.2%) while moving to another house, 4 incidents (3.6%) when the child was alone at home, 2 incidents

(1.8%) when the child woke up at night and the rest 74 incidents (66.7%) happened during daily activities. It was found out that 106 of the corrosive materials (95.5%) were liquid whereas the rest 5 materials (4.5%) were solid. Seventy-five of the corrosives (67.6%) that led to the incidents, we researched, were alkali whereas 33 corrosives (29.7%) were acidic. The form of 3 corrosives (2.7%) could not be identified. Forty-three of the corrosives (50.3%), which had not been in their original bottles were in water bottles, 19 (22%) were in coke bottles, 15 (17.4%) were in soda bottles, 6 (6.9%) were in plastic bins and 3 (3.4%) were in glasses. The corrosive materials were bought from the shops selling unlabelled detergents in 79 incidents (71.2%), from supermarkets in 13 incidents (11.7%), and from peddlers in 11 incidents (9.9%). The purchasing spot could not be identified in 8 incidents (7.2%).

All the victims stayed in the clinic and 77 victims (69.4%) were subject to medical treatment whereas 34 victims (30.6%) were subject to surgical treatment. Forty-seven victims (42.4%) came to the clinic once, 33 victims (29.7%) twice, 10 victims (9%) 3 times, 9 victims (8.1%) 4-10 times and 12 victims (10.8%) more than 10 times for the maintenance of the treatment. Sixty-three of the incidents (56.8%) were treated as a judicial case whereas 48 (43.2%) incidents were not subject to any judicial procedures. We were able to access the judicial reports, prosecution and court recordings of 37 incidents (58.7%), which had been the subject to legal procedures. In examining the judicial reports, it was found out that the trauma endangered the life of the victims in 10 incidents (27%) and rendered the victim unable to follow his ordinary pursuits for 1-5 days in 27 incidents (73%). Also, in examining the prosecution and court recordings, it was found out that the attorney generals decided that there is no need for a legal action in accordance with Article 164 of the Code of Criminal Procedures in 29 incidents (78.4%) and that the offenders judged in Courts of First Instance had been acquitted in 8 incidents (21.6%).

In Christesen's study,<sup>1</sup> 94% of the children subject to a corrosive material accident were under 5 years old. In a research carried out by Dabadie et al,<sup>2</sup> whose sampling group was composed of 100 children, 33 children were the females whereas 67 were males. It was found out that our finding concerning the gender of the children is in conformity with that of Dabadie et al.<sup>2</sup> Considering the literature on child accidents, it is observed that male children are more subject to accidents than female children. Forty-two of the mothers (37.9%) were between 25-28 years on the date of the accident. Gulotta et al<sup>3</sup> states that young



mothers form a risk group in terms of child accidents. It was observed that the mothers of our patients were not among the group of young mothers. The findings of our research conform to the literature emphasizing that the members of the lower socio-economic class are more vulnerable to accident. Since children are permanently at home, it is possible that they are the subject to increased collective accident risks. All the incidents caused by corrosive materials happened accidentally at home. The findings of our research, that accidents usually occurred at home, conform to the findings of Lamireau et al.<sup>4</sup> The findings are also in conformity with the literature. Though all accidents happened at home, the exact place at home varies. Seventy-one incidents (64%) occurred in the kitchen. The kitchen is the most hazardous place for corrosive accidents. The accidents mostly happen during seasonal housecleaning, painting or moving, or when the child is alone at home. The findings of our research are in conformity with those of the literature within this respect. The research of Pollina et al,<sup>4</sup> revealed that 71% of the corrosives leading to an accident were in the liquid form. Our findings support this result as well. It was found out that the cleaning products causing the accident were in their original containers in only 9 of the incidents (8.1%). In the research of Bautista et al,<sup>5</sup> 75% the corrosives were in their original containers whereas this rate was much higher in Agossou and Ayiyi,<sup>6</sup> research (88%), hence, our findings do not support those of the above studies. It is inferred that the main reason of corrosive incidents in our country is selling the products containing corrosives in bottles other than their original containers.

As the literature sets, the best treatment method for all kinds of accidents is precaution. Only 63 incidents (56.8%) were treated as a judicial case although, all incidents had judicial merit. In 48 incidents (43.2%) the liability of informing the legal authorities was not fulfilled since the physicians are unaware of their legal responsibilities. We were able to access the judicial recordings of only 37 incidents (58.7%) of 63 incidents (56.8%), which were tackled as a judicial case. These incidents are within the scope of paragraph 2 and 4 of Article 456 of the Turkish Penal Code. Taking account of the occupational burden and social, economic and cultural status of mothers, the courts decided that there was no need for a legal proceeding due to the fault or negligence of offenders, and they were acquitted in accordance with Article 164 of the Code for Criminal Procedures. It is found out that child accidents caused by corrosives are mostly encountered among male children at the age of 5 and happen due to carelessness and negligence.

The educational status of mothers is a significant factor for the prevention of accidents. The accidents usually happen in summer and in the families whose income level is below poverty line. It is observed that the accidents occurred mostly in the children's own houses and in the kitchen, and during activities such as the one which intervene in the ordinary flow of day including housecleaning or moving to another house and when the children are alone at home.

It is concluded that corrosives were kept in softdrink bottles, soda or water which are normally consumed by children. Approximately 16.2% of these incidents were transferred to our hospital without any medical intervention in the first health institution they were taken, which may result from the lack of physician awareness on their legal responsibilities and lack of experience. Though all the incidents should have been treated as a judicial case and notified to legal authorities, only 56.8% of them were subject to a legal procedure. This proves that physicians neglect the legal aspect of incidents due to their occupational burden.

To summarize, to avoid accident resulting from ingestion of corrosive materials, the following should be kept in mind: 1) We should keep out medicine, detergents, alcohol, aerosol sprays, and any other hazardous chemicals out of the child's reach. Never place such in bottles that would normally be used for drinking or cooking purposes. 2) The arrangements required for selling corrosives in original containers with locked lids should be put in action. 3) Proper and sufficient first aid for the children who are victims of corrosive accidents can decrease the morbidity of incidents. Hence, in-service training aimed at raising the awareness of physicians should be established. It is not possible to distinguish the prosperity of children from social prosperity. The efforts to improve the conditions of child population, which forms 41% of the total population, will contribute to the promotion of social prosperity.

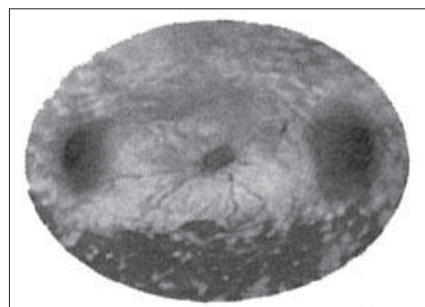
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**Figure 1** - Hysteroscopic view of the fistulous opening.

## An unusual case of colouterine fistula

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Colouterine fistulas (CF) are associated with diverticulitis and trauma of the uterus. Illegal abortions by untrained personnel carry a high risk of complications, including permanent damage to uterus. Infertility or death due to hemorrhage, sepsis, or trauma and perforation of uterus are well-documented.<sup>1,2</sup> Sharma et al reported a 44-year-old obese woman who developed a CF 4 days after hysteroscopic diathermy ablation of endometrium for menorrhagia.<sup>3</sup>

We encountered a case of CF resulting from illegal abortion, 6 years earlier in Delhi. Information regarding the location of past abortion, and any immediate complications was not available. During June 2003, a 30 year-old woman, para 2 (live), with 1 abortion was presented at the Sant Parmanand Hospital, Delhi, India. Following abortion, foul vaginal discharge was experienced, low abdominal pain and secondary infertility. There were no lesions in the genital area or gastrointestinal tract indicative of any tubercular infection. The only abnormality was a restricted uterine motility. On hysterosalpingography, there was irregular uterine cavity, fundal indentations, right tubal cornual block and a partly visualized left tube with no spill. Laparohysterectomy revealed

adhesions between the uterus and the large intestine. Hysteroscopic examination showed thick purulent material in the uterine cavity and normal cornual openings with an additional opening in the uterine fundus (**Figure 1**). The hysteroscopic light through the fundal opening illuminated the bowel as seen on laparoscopy. During laparotomy, adhesions were found between sigmoid colon and uterus with a 4 mm fistulous tract. The tract was dissected and cut while the uterine perforation was closed with 2-0 vicryl and the colon sutured with 3-0 silk. An omental flap was interposed between the uterus and the colon. During chemopertubation, the sealed fistula site was visualized and there was a blockage at the fimbrial end of the dilated left tube. A fish-mouth fimbrioplasty was carried out. The postoperative phase, including the 2-year follow-up, has been uneventful with no vaginal discharge or abdominal pain.

Actual statistics regarding the global incidence and complications of illegal abortions might not be available, while unfortunate victims would hunt for rational therapeutic interventions from a competent professionals. A clinical diagnosis of any large-sized CF is achievable through a demonstration of fecal matter at the introitus. Recently, sonohysterography was employed to diagnose CF in Japan by demonstration of flow of ultrasound contrast medium between uterine cavity and sigmoid colon through posterior wall of the uterus.<sup>4</sup> Nevertheless, endoscopes aid in the diagnosis of any small-sized CF. As evident in the present case, the hysteroscopic opening in the uterine fundus (**Figure 1**) was the unequivocal evidence.

Clinicians are bound to treat the survivors of abortions with resident sequelae. While doing so, they should pick up small-sized fistula through hysteroscopy. That should not be a problem since hysteroscopes are so thin that they would fit through the cervix with minimal or no dilatation. Furthermore, diagnostic hysteroscopy, including simple operative hysteroscopic manipulations, can be accomplished with local anesthesia in any office setting. Any complex operative laparohysterectomy procedures would need to be carried out in an operating room.



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## Peritoneal tuberculosis mimicking ovarian pathology. A series of 11 cases

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Tuberculous peritonitis is one of the common forms of extrapulmonary tuberculosis that is endemic among socioeconomically disadvantaged communities in both developing and developed countries. The increase in the incidence of abdominal tuberculosis may be related to factors like immigration, acquired immunodeficiency syndrome and socioeconomic deprivation.<sup>1</sup> Several reports have suggested that peritoneal tuberculosis can mimic advanced ovarian cancer and is a rare gynecologic condition that presents to gynecologists and oncologists with ascites, a pelvic mass and elevated CA-125.<sup>2</sup> We aimed to present the clinical, laboratory, ultrasound (US) and computed tomographic (CT) findings of 11 patients with elevated CA-125 levels mimicking benign or malignant ovarian pathologies suffering from tuberculous peritonitis.

In a study of 11 women presenting with an adnexal solid or cystic mass, elevated CA-125, and with or without ascites mimicking benign or malignant ovarian pathologies underwent surgical operations for presumed benign or malignant ovarian pathologies at the Department of Obstetrics and Gynecology,

Dicle University School of Medicine, Diyarbakir, Turkey from January 1, 2000 to October 31, 2004. All patients underwent clinical examination, laboratory tests such as whole blood cell count, biochemical and urine analysis, erythrocyte sedimentation rate (ESR), tumor markers, biochemical analysis of ascites such as albumin, lactate dehydrogenase (LDH), glucose, lymphocyte count and microbiological analyses of ascites were carried out. A skin test was also performed with a purified protein derivative (PPD) of old tuberculin in patients with ascites, PPD was read as positive if the induration measured  $\geq 10$  mm. A chest x-ray was carried out in all of the patients. Upper gastrointestinal endoscopy and colonoscopy of patients who had ascites were also examined. All the patients were examined with US of the abdomen and pelvis, of which 8 also underwent CT scans. Peritoneal tissue was obtained from 10 women by laparotomy and one woman by cervical lymph node biopsy. Pathology of 11 women revealed tuberculous peritonitis. The age of 11 women with tuberculous peritonitis at presentation ranged from 17 - 48 years (mean  $32.33 \pm 10.03$  SD). The most common symptoms were abdominal pain that occurred in 100% of patients and swelling in 63% of patients. Constitutional symptoms were also common. Purified protein derivative skin test was positive in 4 patients (50%). White blood cell count (WBC) was normal in all patients [11 (100%)], with a normal differential. Erythrocyte sedimentation rate was higher than 50 mm/h in 6 (54.5%) of patients and ESR was lower than 50 mm/h in 5 (45.4%) of patients. Normochromic normocytic anemia was present in 9 cases (81.8%). The CA 125 levels were high in all the patients and ranged from 212 - 556 IU/ml (mean  $322.72 \pm 93.45$  IU/ml). An abnormal chest x-ray, suggestive of previous tuberculosis was present in 2 patients. Abdominal and pelvic sonography and computerized tomography findings of all patients are presented in **Table 1**. Ascitic fluid was obtained from 8 (72%) of cases and was yellowish, turbid and opalescent. The other 3 cases had no ascites (28%). Ascitic fluid analysis revealed a low serum ascites albumin gradient ( $<1.1$  g/dL) with a high lymphocyte count in all 8 patients. Ascitic fluid glucose was less than 70 mg/dl in only 2 cases (25%). Lactate dehydrogenase (LDH) levels ranged from 115 - 257 mU/ml (mean 168 mU/ml). The ascitic smear (Ziehl-Neelsen stain) and culture of ascitic fluid for *Mycobacterium tuberculosis* were negative in all 8 of patients. Upper gastrointestinal endoscopy and colonoscopy of patients who had ascites were normal. Laparotomy was performed in 10 patients and cervical lymph node biopsy was performed in one patient, and findings of tuberculous

## Peritoneal tuberculosis

**Table 1** - Abdominal and pelvic sonography, CT and operative findings and CA-125 levels of patients with tuberculous peritonitis.

Case	Age	Abdominal and pelvic sonography findings	Abdominal and pelvic CT findings	CA 125 level (u/ml)	Operative findings
1	17	Ascites, 4 × 4 cm septated cystic mass in the right adnexa and 2 × 8 cm semisolid mass in the left ovary	Ascites, omental thickening, 4 × 4 cm septated cystic mass in the right adnexa and 10 × 5 multiloculated cystic mass in the pouch of Douglas	556	Ascites, omental mass, multiple small granules covering all peritoneal surfaces involving, intestinal loop fallopian tubes, uterus and ovaries, dense adhesions between ovaries, fallopian tubes and pelvic side wall and right tubo-ovarian abscess
2	22	18 × 14 × 10 cm septated cystic mass in the right ovary		388	20 cm abscess formation between right over and pelvic side wall, white granulomatous lesions on uterus, left adnexa and intestinal loops
3	27	Ascites, 5 × 5 cm cystic mass in the right ovary	Ascites, omental thickening, 7 × 6 cm cystic mass in the right ovary	321	Ascites, miliary granules covering all peritoneal surfaces involving, intestinal loop fallopian tubes, uterus and ovaries, 5cm cystic adnexal mass
4	27	5 × 5 cm cystic mass in the left ovary, 4 × 4 cm cystic mass in the right ovary and suspicion of ovarian torsion (High impedance PI>1.5 and RI>0.6 in arterial flow and absent venous flow in the right ovary with using transvaginal color Doppler sonography)		375	5 cm right tubo-ovarian abscess and 4 cm left ovarian cyst miliary granules seeded over all peritoneal surfaces
5	28	Ascites and 7 × 8 cm cystic mass in the left ovary	Ascites and 7 × 8 cm cystic mass in the left ovary	291	Ascites, multiple small granules covering all peritoneal surfaces involving, intestinal loop fallopian tubes, uterus. Adhesions of intestine and uterus. Normal appearance of ovaries
6	36	Ascites, hepatomegaly, splenomegaly, para-aortic and peripancreatic lymph and nodes, 6 × 6 cm solid mass in the right ovary, enlarged left ovary and irregularity of the surface of the left ovary	Ascites, hepatomegaly, splenomegaly, para-aortic and peripancreatic lymph nodes, 6 × 6 cm solid mass in the right ovary, enlarged left ovary and irregularity of the surface of the left ovary	269	Cervical lymph node biopsy
7	36	Ascites, bilateral hydrosalpinges, 5 × 7 cm hypoechoogenic irregular solid mass adjacent to the right ovary	Ascites, 6 × 7 cm irregular solid mass adjacent to the right ovary	280	Ascites, bilateral, miliary granules covering all peritoneal surfaces involving, intestinal loop fallopian tubes, uterus and ovaries, Hydrosalpinges, large omental mass
8	43	Ascites, 8 × 7 cm complex mass in the right ovary	Ascites, peritoneal and omental thickening, 8 × 5 cm cystic mass with nodular lesions in the right ovary	247	Ascites, omental mass, multiple small granules covering all peritoneal surfaces involving, intestinal loop, fallopian tubes, uterus and ovaries, Adhesions of omentum, small intestine and transverse colon. Adhesions of ovaries, fallopian tubes and pelvic side wall.
9	47	Ascites and 5 × 5 cm solid mass in the left ovary	Ascites, hepatomegaly, splenomegaly, 5 × 5 cm solid mass in the left ovary	212	Ascites, miliary nodules throughout peritoneal cavity, ovaries, fallopian tubes, dense and diffuse adhesions in peritoneal and pelvic cavity
10	48	Ascites, hepatomegaly and 5 × 4 cm multiloculated cystic mass in the left adnexa	Ascites, hepatomegaly, and 5 × 4 cm cystic mass in the left ovary	334	Ascites, miliary nodules, throughout peritoneal cavity, ovaries, fallopian tubes, dense and diffuse adhesions in peritoneal and pelvic cavity
11	27	7 × 7 cm ovarian cyst with appearance of endometrioma		277	Miliary nodules, throughout peritoneal cavity, ovaries, fallopian tubes, dense and diffuse adhesions in peritoneal cavity and between ovaries, fallopian tubes and pelvic side wall

peritonitis are presented in **Table 1**. Histology revealed granuloma containing giant Langhans type cells and central necrosis compatible with tuberculosis in all patients. The standard 4-drug therapy of isoniazid (INH) (5 mg/kg), rifampicin (10 mg/kg), ethambutol (15 mg/kg) and pyrazinamide (25 mg/kg) were administered as a first-line treatment, continued for a total of 2 months, followed by 2-drug antituberculous treatment (rifampicin/INH) for 4 months. All cases were called for periodic controls every month during the whole treatment period.

Tuberculous peritonitis in developed countries is a rare condition due to the good health conditions,

pasteurization programs, new and more effective anti-tuberculosis chemotherapy agents and better hygiene conditions but is seen mainly among the immigrant populations and in patients with AIDS. However, in developing countries, all types including abdominal tuberculosis are still an important medical problem due to the poor health conditions and socioeconomic deprivation.<sup>1</sup> Tuberculous peritonitis results from reactivation of latent tuberculous foci in the peritoneum or from the hematogenous spread from a primary infection in the lungs. The primary focus usually heals completely, leaving no clinical and radiological evidence of a lung lesion

and a normal chest radiograph does not exclude the diagnosis.<sup>2-5</sup> An abnormal chest x-ray, suggestive of previous tuberculosis was present in our 2 patients. Tuberculous peritonitis can be seen in subjects of any age.<sup>3</sup> The age of our study group ranged from 17 - 48 years. Abdominal pain, abdominal swelling, weight loss, night sweats, fever are the most common presentation of tuberculous peritonitis and abdominal tenderness, ascites and a palpable abdominal mass are the most common findings on physical examination.<sup>4</sup> In our patients, abdominal pain (100%), ascites (72%) and abdominal swelling (63%) are the most common presentation of tuberculous peritonitis. Elevated erythrocyte sedimentation rates, a low serum-ascites albumin gradient (<1.1 g/dL) and normochromic normocytic anemia often accompany tuberculous peritonitis but are of limited diagnostic importance in view of their non specificity.<sup>1-5</sup> Microbiological investigations of ascitic fluid cannot be considered reliable. Ziehl-Neelsen staining of ascitic fluid often gives negative results. The positive culture rate of peritoneal fluid ranges from 0 - 63% in reported series.<sup>4</sup> We did not find acid-fast bacilli in the ascitic fluid and positive cultures in our cases. The increase of CA-125 levels in tuberculous peritonitis has been documented in the literature and the serum CA-125 increase is a true association with tuberculous peritonitis.<sup>5</sup> We found high levels of CA-125 in all our patients and ranged from 212 - 556 IU/ml (mean 322.72 ± 93.45 IU/ml).

The presence of sonographic and CT findings of tuberculosis peritonitis and increased serum CA-125 antigen might mimic malignant ovarian pathologies.<sup>2</sup> The presence of sonographic and CT findings of tuberculosis peritonitis of our 8 (72%) cases with ascites are similar to those of ovarian cancer, is a primary diagnostic consideration. Immediate exploratory laparotomy was made in one of our case with a suspicion of right ovarian torsion and found right tubo-ovarian abscess with miliary granules seeded over all peritoneal surfaces (case 4). The other case with septated cystic mass (18 × 14 × 10 cm) with sonography findings in the right ovary without ascites was found 20 cm abscess formation between right over and pelvic side wall, with granulomatous lesions on exploratory laparotomy (case no. 2). The appearance of endometrioma with sonography findings in our case is another interesting finding with tuberculosis peritonitis (case no. 11). Laparotomy were performed in 10 patients and cervical lymph node biopsy were performed in one patient. Histology revealed granuloma containing giant Langhans type cells and central necrosis compatible with tuberculosis in all patients. All patients responded well to antituberculous therapy.

The presence of sonographic and CT findings and increased serum CA-125 levels, as in our cases, are not sensitive markers for ovarian cancer and a high index of suspicion for tuberculous peritonitis with genital tract involvement needs to be maintained, especially in high risk groups such as immigrants from tuberculosis endemic areas, in patients with AIDS, in persons who have low socioeconomic status. In our study, we also emphasize that tuberculous peritonitis not only mimics ovarian cancer but also benign ovarian pathologies such as ovarian torsion and endometrioma.

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## Cardiopulmonary resuscitation in pregnancy

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Cardiac arrest in pregnancy is rare and it has been reported to occur once in every 30,000 pregnancies.<sup>1-3</sup> Almost 10% of maternal deaths result from cardiac arrest. We knew that more than half of resuscitation attempts in the non-pregnant population were unsuccessful. Tragically, even when cardiac



activity is restored, only half of ventricular fibrillation cardiac arrest victims admitted to the Emergency Department survived. This means that 3 out of 4 cardiopulmonary resuscitation (CPR) attempts will be unsuccessful.<sup>2</sup> When a pregnant woman goes into cardiac arrest, more than one life is at stake.<sup>4</sup> Attempts to CPR during pregnancy may be impeded by the physiologic changes that take place during pregnancy, including the gravid uterus. Therefore, the obstetrician/gynecologist must understand the physiologic changes that occur in pregnancy and affect the potential for resuscitation.<sup>2,3,4</sup> After this review, one should understand the effect of pregnancy on resuscitation efforts and have a basic understanding of the efforts needed to resuscitate the gravid patient. In addition, we will discuss perimortem cesarean and its effect on maternal and fetal outcome.<sup>2</sup>

***Influence of cardio respiratory changes in pregnancy on resuscitation.*** Cardio respiratory changes that take place in pregnancy include alterations in blood volume, heart rate, blood pressure, stroke volume, cardiac output, systemic vascular resistance, minute ventilation, and functional residual capacity (FRC). An understanding of these changes and their significance is important when managing the pregnant patient in cardiac arrest. At term plasma, volume averages 40-50% above non-pregnant values. Red cell mass also increases by 20%, but the increase is relatively less than the increase in plasma volume, only by approximately 30%, resulting in a physiologic anemia of pregnancy.<sup>2,4,5</sup> During maternal cardiac arrest, this physiologic anemia may have an impact on oxygen delivery to vital organ systems, including the heart, brain, uterus and fetus.<sup>2,5</sup> Cardiac output is also increased, by 35-40% during gestation.<sup>2,4,5</sup> Uterine blood flow is maximally increased and accounts for 10% of the cardiac output during the third trimester.<sup>2,4</sup> This massive shunting of blood to the uterus may hinder efforts at CPR.<sup>5</sup> In the other hand, aortocaval compression from the enlarged uterus in the second half of pregnancy; impede resuscitation efforts by diminishing forward flow as well as venous return. This significant decline in venous return result in a decline in cardiac output, and a 20-30% decrease in mean arterial pressure.<sup>1,2,4</sup> A maternal systolic blood pressure of <80 mm Hg is inadequate to perfuse the uterus. This can be significantly detrimental during CPR, when the anticipated amount of cardiac output from the chest compression is only 30% in the non-pregnant individual. In addition, the gravid uterus exerts pressure on the diaphragm, which impedes the ability to achieve forward blood flow during chest compression.<sup>2,3</sup> Cardiopulmonary resuscitation in the non-pregnant individual generally does not

achieve more than 30% of a normal cardiac output. A pregnant woman will probably not achieve even this level of cardiac output. Uterine blood flow is maximal and cannot be increased during hypoxic, low-flow conditions; thus, there will be vasoconstriction in the uteroplacental bed, further compromising the fetus.<sup>2</sup> Minute ventilation increases during pregnancy secondary to an increase in tidal volume, which results from progesterone's effect on the respiratory drive. A decrease in the FRC is resulted from the enlarging uterus impinging on the diaphragm. This decrease in FRC, along with the increase in oxygen demand secondary to the gravid uterus and fetus, predisposes the pregnant woman to a rapid decrease in oxygen saturation during periods of hypoventilation. The increase in minute ventilation that occurs in pregnancy leads to a compensated respiratory alkalosis. To keep the maternal pH within normal range, the kidneys excrete bicarbonate.<sup>2,5</sup> Oxygen consumption is markedly increased during pregnancy (by 20%) secondary to the increased needs of the uterus, placenta, and fetus, as well as increased maternal needs.<sup>2,5</sup> During cardiac arrest, increased maternal hypercarbia will lead to fetal acidosis, and vasoconstriction in the uteroplacental circulation will rapidly lead to hypercarbia and hypoxia in the fetal compartment.<sup>2</sup>

During pregnancy, the basal metabolic rate is markedly increased, and therefore, there is an increased production of carbon dioxide. When there is a lack of maternal carbon dioxide exchange, rapid development of maternal acidosis makes it more difficult to achieve resuscitation.<sup>2</sup> Also, during pregnancy, there is a decrease in gastrointestinal motility, an increase in gastric emptying time, and relaxation of the lower esophageal sphincter. This significantly increases the risk of aspiration during CPR.<sup>1,4</sup> When the pregnant woman's airway is unprotected and ventilation is being effected, either with mouth-to-mouth ventilation or mask-to-mouth ventilation, there is a risk that high-pressure ventilation can lead to air filling the stomach, resultant vomiting and aspiration.<sup>2</sup> Therefore, the primary goal of the resuscitation efforts should be establish a stable airway as quickly as possible, preferably with endotracheal intubation. If intravenous access has not been established, medications can be given via the endotracheal tube. The atropine, lidocaine, or epinephrine can be administered through the tracheal tube.<sup>2</sup> Due to the increase in distribution that occurs during pregnancy, drugs used for resuscitation may not be as effective. An additional consideration is that alpha-adrenergic agents and combined alpha, and beta agonists may produce uteroplacental vasoconstriction,

which leads to a decrease in fetal oxygenation and fetal carbon dioxide exchange.<sup>2</sup> All the above-mentioned physiologic and anatomic changes impede the resuscitative efforts of the pregnant woman.

**Modifications of Basic life support (BLS) and Advanced life support (ACLS) in pregnancy.**

**Basic life support:** 1) Airway - a clear airway must be quickly established with the head tilt-jaw thrust, or the head tilt-chin lifts the maneuver and then maintained. Suction should be used to aspirate vomit. Badly fitting dentures and other foreign bodies should be removed from the mouth, and an airway should be inserted. These procedures should be performed with the patient inclined laterally, or supine and the uterus displaced as described below.<sup>1,2</sup> 2) Breathing - if the patient is not breathing adequately, intermittent positive pressure ventilation should be started once. The airway has been cleared; mouth to mouth, mouth to nose, or mouth to airway ventilation should be carried out until a self-inflating bag and mask are available. Ventilation should then be continued with 100% oxygen and a reservoir bag. Due to the increased risk of regurgitation and pulmonary aspiration of gastric contents in late pregnancy, cricoid pressure should be applied until the airway has been protected by a cuffed tracheal tube.<sup>1</sup> Observing the rise and fall of the chest in pregnant patients are also more difficult. 3) Circulation - Circulatory arrest is diagnosed by the absence of a palpable pulse in a large artery (carotid or femoral). Chest compressions are given at the standard rate and ratio of 15:2. Chest compression on a pregnant woman is made difficult by flared ribs, raised diaphragm, obesity, and breast hypertrophy. As the diaphragm is pushed upwards by the abdominal contents, the hand position for chest compressions should similarly be moved up the sternum, although currently no guidelines suggest exactly how far.

In the supine position, an additional factor is compression of the inferior vena cava by the gravid uterus, which impairs the venous return and reduces cardiac output; all attempts at resuscitation will be futile unless the compression is relieved. This is achieved either by placing the patient in an inclined lateral position by using a wedge or by displacing the uterus manually.<sup>2,4</sup> Raising the patient's legs will improve the venous return. 4) Lateral displacement of the uterus - effective forces for chest compression can be generated with patients inclined at angles of up to 30°, but the pregnant women tend to roll into a full lateral position when inclined at this angles, making chest compression difficult. The Cardiff resuscitation wedge is not a commercially available techniques, which we need to use. One technique is the "human wedge," in which the patient is tilted onto a knee

to provide a stable position for basic life support.<sup>1,2</sup> The human wedge has an advantage in that it can be used without equipment, using an untrained person.<sup>2</sup> However, its disadvantage is that the wedge must be displaced when defibrillation is necessary.<sup>2</sup> Left lateral displacement of the gravida during resuscitation may impede and decrease the effectiveness of chest compression.<sup>2</sup> Alternatively, the patient can be tilted onto the upturned chair. Purpose-made wedges are available in maternity units, but any cushion or pillow can wedge the patient into the left inclined position. An assistant should, however, move the uterus further to the inferior vena cava by lifting with 2 hands to the left and to the patients' head.<sup>1,4</sup>

**Advanced life support:** 1) Intubation - tracheal intubation should be carried out when facilities and skill are available. Difficulty in tracheal intubation is more common in pregnant women and specialized equipment for advanced airway management may be required. A short obese neck and full breasts due to pregnancy may make it difficult to insert the laryngoscope into the mouth. The use of a short handled laryngoscope or one with its blade mounted at more than 90° (polio or adjustable demounting the blade from the handle during insertion into the mouth may help).<sup>1,4</sup> Mouth to mouth or bag and mask ventilation is best carried out without pillows under the head and with the head and neck fully extended. The position for intubation, however, requires at least one pillow to flex the neck and extend the head. Any pillow removed to facilitate initial ventilation must, therefore, be kept at hand for intubation. In the event of failure to intubate the trachea or ventilate the patient's lungs with a bag and mask, insertion of a laryngeal mask airway should be attempted. Cricoid pressure must be temporarily removed in order to place the laryngeal mask airway successfully. Once the airway is in place, cricoid pressure should be reapplied.<sup>1</sup> Another considerable point is that chest thrusts instead of abdominal thrusts should be used during maternal resuscitation for airway obstruction.<sup>2</sup> 2) Defibrillation and drugs- there is little information regarding the use of the pharmacologic agents is ACLS during pregnancy. However, current recommendations are that ACLS protocols are followed in pregnancy as they are in the non-pregnant individual.<sup>1,2</sup> On a practical note it is difficult to apply an apical defibrillator paddle with the patient inclined laterally, and great care must be taken to ensure that the dependent breast does not come into contact with the hand holding the paddle. This problem is avoided if adhesive electrodes are used.<sup>1</sup> Increasingly, magnesium sulphate is used to treat and prevent eclampsia. If a high serum magnesium concentration

has contributed to the cardiac arrest, consider giving calcium chloride. Tachyarrhythmias due to toxicity of the anesthetic drug bupivacaine are probably best treated by electrical cardioversion or with bretylium instead of lidocaine (lignocaine).<sup>1</sup> There are theoretical concerns with the use of alpha-adrenergic agents and the effect on uteroplacental blood flow. Lidocaine theoretically can induce fetal acidosis; it does not appear to cross the placenta. Beta-blockers can induce fetal bradycardia; however, no adverse fetal effects have been documented. An additional consideration is that rapid maternal resuscitation offers the best chance of survival for both mother and fetus.<sup>2</sup> 3) Cesarean section - if CPR and emergency resuscitation interventions have continued for 4-5 minutes without success, and the fetus was beyond the viability (24 weeks of gestation or greater), a perimortem cesarean delivery must be considered. Decisions regarding delivery should be made by 4 minutes in the code, and delivery of the baby accomplished by 5 minutes.<sup>2,3,4</sup> It helps to save the life of both the mother and the baby. By delivery of the fetus, occlusion of the inferior vena cava is relieved completely, whereas it is only partially relieved by manual uterine displacement or an inclined position. However, it improves thoracic compliance and chest compression and also intra-thoracic pressure is relieved and made an increase of 25-50% in the circulating blood volume after the uterus is emptied and auto transfusion occurs.<sup>2,4</sup> After cardiac arrest, non-pregnant adults suffer irreversible brain damage from anoxia within 3-4 minutes, but pregnant women become hypoxic more quickly. Although, evidence shows that the fetus can tolerate prolonged periods of hypoxia, the outlook for the neonate is optimized by immediate cesarean section.<sup>1</sup>

Several case reports document the successful resuscitation of pregnant woman in cardiac arrest after perimortem cesarean section. The time interval from cardiac arrest to delivery is probably the single most important prognostic factor for fetal survival. If the fetus is delivered within 5 minutes of maternal cardiac arrest, intact neurologic survival is markedly increased.<sup>2,4</sup> However, only 25% of fetuses will survive neurologically intact even as long as 35 minutes after maternal cardiac arrest.<sup>2,4</sup> Therefore, during CPR, to maximize maternal and fetal survival, the 4 minute interval from arrest to initiating delivery should be considered.<sup>2</sup> Before performing a cesarean section, gestational age should be estimated based on last menstrual period, fundal height, or previous ultrasound evaluation. Attempts to document fetal viability or gestational age by ultrasound examination during CPR are unwarranted as the time required

to perform an ultrasound examination would be detrimental and the examination would be awkward during attempts at CPR.<sup>2</sup> The ACLS and CPR should continue during cesarean delivery to maximize cardiac output, perfusion of maternal organ systems, and uteroplacental perfusion.<sup>1,2</sup>

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## Is there any effect of age, gender and body mass index on the electrocardiographic T-wave amplitude in Northern Saudi Arabia?

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Variation in the normal pattern of electrocardiogram (ECG) has been extensively studied, and it has been found that T-wave inversion, ST segment depression, ST segment elevation, peaked tall T-wave and early repolarization pattern are more prevalent in certain ethnic groups.<sup>1-3</sup> However, a tall T-wave may not be suggestive of transmural ischemia in Saudi population, as we do not know the normal limits of T-wave amplitude in this population. Even in some of the studies carried out so far, there is some controversy regarding these variations in different ethnic groups as there is some effect of age and gender on ECG.<sup>4</sup>

In our study, we measured T-wave amplitudes of the ECGs of healthy adults of north zone with similar



environmental conditions. The primary purpose of this study was to quantify the normal T-wave amplitude limits according to the gender, age and body mass index (BMI) in Saudi population of northern region. This was a cross-sectional study conducted in the northern region of the Kingdom of Saudi Arabia in 2 stages. In the first stage, we randomly selected 1380 subjects, registered at primary health care centers from the 3 main cities of northern region. We included 1091 subjects in the study and we divided them into 4 sub-groups according to their ages and BMI. On the basis of medical record and history obtained, subjects were excluded if they had any history of hypertension, diabetes mellitus, chronic airway disease, chronic anemia, connective tissue disease or chronic use of any kind of medicine.

During the second stage of the study the resting ECGs were recorded in supine position by trained and licensed technicians using a 3-channel machine (Hewlett-Packard, Pagewriter Xli Model M1700A). Integrated software demonstrated the interpretation of all these ECG recordings. Only those individuals with normal findings on both the echocardiography and the stress ECG were included in the study. All were reviewed and wave amplitude was measured manually by one of the authors using Minnesota codes definitions and standards of measurements.<sup>5</sup>

The mean T-wave amplitude in inferior leads (II, III, aVF) for each individual was calculated as a single value. Likewise, the T-wave amplitude in each of the pairs of leads (I, aVL), (V3, V4) and (V5, V6) was also calculated as a single value for each pair, to limit the number of variables. The T-wave amplitude in leads V1 and V2 were measured separately due to marked differences in the values. The T-wave amplitude was approximated to the closest 0.25 mm (based on the calibration of the ECG paper of 1 mV=10 mm). The T-wave was considered biphasic when the negative was >1 mm. The Sokolow-Lyon voltage (the sum of the amplitude of the S wave in lead V1 and the amplitude of R wave in lead V5 or V6, whichever is greater) was also measured for each individual.<sup>1</sup> The standard methods of performing ECG, standard procedures for measurement of wave patterns, and classification of ECG abnormalities have been compiled together as Minnesota coding of ECG. Analysis of results for male and female subjects was carried out separately for each group. One-way analysis of variance (ANOVA), Kruskal-Willis, and Chi-square test were used.

For both males and females subjects, when compared for age, there was significantly lower heart rate in younger age groups as compared with the old age groups. Similarly for the Sokolow-Lyon voltage,

there was a statistically significant difference among the younger age groups as they have higher values than the older age groups. When these parameters were compared for BMI, we found statistically significant difference in heart rate, as lower BMI was associated with lower heart rates for males where it was non-significant for females. The Sokolow-Lyon voltage was significantly lower for both males and females in lower BMI groups (**Table 1**).

Overall T-wave amplitude was greater in men than in women in all leads. While there was significant decrease in median of T-wave amplitude as the age increases in males in leads I-aVL and II, III, aVF groups but, it was non-significant in leads V1 and V2. Additionally, it was statistically significant in leads V3-V6 for males as the age advances (**Table 1**). This trend was not there when females were compared for their age and T-wave amplitudes as it was significant only in chest leads V2- V6. When T-wave amplitude was compared with BMI of males and females, the amplitude decreased significantly in both as the BMI increased. This trend was more marked in chest leads V2-V6. There was similar decrease in T-wave amplitude in leads I, aVL for males and non-significant in leads II, III, aVF. The reverse was true for the female; namely, it was significant in leads II, III aVF and non-significant in leads I, aVL (**Table 1**). There was no significant difference in T-wave height in lead V1 among groups. Biphasic T-waves were present in 12 males in leads V1 and in 6 males in lead V2 whereas it was present in 7 females in leads V1 and 2 in leads V2. There was no specific relation to age or the BMI in all these subjects with biphasic T-waves as these were distributed randomly in all groups.

Few studies have been carried out on other ethnic groups, which also exhibit that there are statistically significant differences in the ECG parameters in different ethnic populations.<sup>2,4</sup> Our study addresses the issue of normal limits of T-wave amplitude and effect of age, gender and BMI on it especially in the population of northern region, Kingdom of Saudi Arabia. We found out that Sokolow-Lyon voltage differs among different age groups in both males as well as females although, it was more marked in males as some other studies showed other ethnic groups.<sup>1,6</sup> While the similar patterns have been demonstrated as regard to different age groups. Likewise, Sokolow-Lyon voltage decreased as the BMI increased among our subjects showing that there is a marked relationship between the BMI and the QRS voltage. One of the suggested reasons for this relationship of BMI, and the QRS voltage is the thoracic diameter. Some studies reported that African Americans have smaller thoracic diameter than Caucasians and as

**Table 1** - Median value of T wave height in mm in different age groups and body mass index of Saudi males and females.

Outcome variables	Males/females independent variables (Age groups)				Level of significance Male/female
	15-24	25-34	35-44	45-55	
Average in I-aVL	2 / 1	1.75 / 1	1.50 / 1	1.50 / 1	<i>p</i> <0.05 / NS
Average in II, III, aVF	1.5 / 1.25	1.25 / 1.25	1.25 / 1.25	1 / 1	<i>p</i> <0.05 / NS
Average in V1	0.25 / 0.25	0.0	0.0	0.25 / 0.25	NS* / NS
Average in V2	6.5 / 3.5	6 / 3	6 / 3	5.5 / 2	NS / <i>p</i> <0.05
Average in V3-V4	6 / 3	5.5 / 2.5	5 / 2	4.5 / 2	<i>p</i> <0.05 / <0.01
Average in V6-V6	4 / 3.5	4.25 / 3	3 / 2.5	2.75 / 2.5	<i>p</i> <0.05 / <0.05
	Males/females body mass index (M <sup>2</sup> /Kg)				
	18.5-24.9	25-29.9	30-34.9	>35	
Average in I, aVL	1.75 / 1.25	1.75 / 1.25	1.50 / 1	1.50 / 1	<i>p</i> <0.05 / <0.05
Average in II, III, aVF	1.5 / 1.25	1.5 / 1.25	1 / 1	1.25 / 1.25	NS / <0.05
Average in V1	0.25 / 0.25	0.25 / 0.25	0.0	0.0	NS / NS
Average in V2	7 / 4	6 / 3.5	5.5 / 3	5 / 2	<i>p</i> <0.05 / <0.05
Average in V3-V4	6.5 / 3.5	6 / 2.25	5.5 / 2	4.5 / 2	<i>p</i> <0.05 / <0.01
Average in V5-V6	4.5 / 4	4 / 3	3 / 3	3 / 2.5	<i>p</i> <0.05 / <0.05
NS - non-significant					

the thoracic diameter decreases, pre-cordial ECG voltage may increase.<sup>7</sup> The relationship between QRS complex and the ethnic groups are confounded by the prevalence of diseases, such as hypertension that may affect the QRS voltage. However, in our study we tried to minimize this effect as we included only normotensive individuals.

The incidence of T-wave changes varies among the different ethnic groups,<sup>1,4</sup> but there are few studies which reinforced our study's results that revealed T-wave amplitude was higher in younger age groups. Although, differences in T-wave patterns among ethnic groups are usually reported according to the Minnesota Codes. However, all anterior leads (V1-V5) are grouped together in the coding system, whereas, in our study we found differences in T-wave amplitudes in leads V3-V6 in both males and females when compared in respect of age groups and the BMI.

The T-wave amplitude was significantly low in leads II, III, aVF in females in all groups as compared with the males in similar groups. Walker and Walker<sup>8</sup> have noticed no ethnic difference T-wave height in lead V1 as it was very small, and in our study the median T-wave height in leads V1 was also very low so the value may not be statistically significant, comparable to that study.<sup>9,10</sup> Thus, individuals with lower BMI had the highest median T-wave amplitude in leads V2-V6, and the individuals with higher BMI have the lowest T-wave amplitude. Lower T-wave amplitude may increase the likelihood of having the flat or inverted T-waves. A biphasic T-wave, however,

was an uncommon finding in our study in leads V1 and V2 with no predilection to either age or the BMI of the individuals. The reason of this biphasic T-wave may be overall very low amplitude of T-wave in this lead. In one study, these abnormal T-wave were due to increase resting sympathetic tone and not due to organic heart disease in most asymptomatic patients as these tend to disappear with exercise.

In conclusion, there is an effect of BMI, gender and different age groups on amplitude of T-wave; therefore, more large scale studies should be conducted to standardize the amplitude of T-wave in the Saudi population.

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## Densitometric analysis of Dot blot assays for human immunodeficiency virus type 1 and 2 antibodies

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The demonstration of an antibody response specifically directed against HIV proteins is accepted as evidence of infection. Serological studies have shown, following infection, patients develop antibodies to both Gag and Env proteins, but the qualitative and quantitative differences in the immune response occur between individuals. Antibodies to individual HIV-1 and 2 proteins can be detected by Dot blot (DB) assay using recombinant Gag and Env proteins.<sup>1</sup> Dot blot provides highly specific results, but they are usually not reliable for quantification antibody production. The need for a more objective DB assay to better define the immune status against HIV antigens promoted us to develop a quantitative DB assay.<sup>2,3</sup> This report describes DB assays that enable us to determine the antibody response against single HIV antigens by using a computer-assisted densitometer for image analysis.

**Human sera.** The study was conducted on the sera of 110 Iranian patients who were confirmed

HIV-1 positive; asymptomatic HIV-infected subjects, HIV-infected intravenous drug users and hemophilic infected subjects collected in 2002 - 2003, as well as 15 HIV-2 positive samples were obtained from Pasture Institute of Iran. A total of 180 samples from healthy blood donors were also obtained.

**Recombinant HIV antigens.** Recombinant antigens were cloned and expressed in *Escherichia coli* BL21 DE3 and highly purified as described elsewhere.<sup>4</sup>

**Dot blot procedure.** Recombinant antigens p24, gp41, gp120 and gp36 were diluted to optimal concentrations, in a 20 mM Tris buffer (coating buffer). A 5 µg sample of an antigen was pipetted into each dot in a Horizontal row of a Nitrocellulose strip (Hybond C; Amersham Pharmacia Inc., Sweden). Vertical rows, A contained the antigen p24, B with gp41, C with gp120, and D with gp36 antigens, while row G was coated with 50 ng per dot of human immunoglobulin G (Sigma-Aldrich Inc., Germany) and row H was dotted with coating buffer only. After incubation overnight at 4°C, the strips were washed once with 1 ml of 20 mM Tris buffer saline (TBS), pH 7.2. Blocking (1 g of BSA in 100 ml of TBS) was added, followed by an hour of incubation at room temperature during which the plates were rotated on a platform. The strips were washed once with TBS-Tween 20. Each serum sample to be tested was diluted 1:100 with sample diluent (TBS-Tween 20) and allowed to stand for 30 minutes at 20°C. The first 2 columns of the plate was reserved for positive and negative control samples. Diluted sera were pipetted onto each strip and incubated for 45 minutes at 37°C. Strips were rinsed twice with TBS-Tween 20, and incubated with 800 µl of a 1:2,000 dilution of alkaline phosphatase-conjugated goat anti-human immunoglobulin G (Sigma-Aldrich, Inc., Germany). Strips were rinsed twice with TBS-Tween 20 and incubated with BCIP/NBT substrate (Sigma-Aldrich, Germany) for 10 minutes at 37°C in the dark chamber. Membranes were washed in water and air-dried. Analysis of the results was accomplished by capturing the strip images, measuring the Density of Reflectance (DR) of anti-p24, -gp41, -gp120 and -gp36 antigen dots, and calculating the relative intensity (RI) by a video densitometer (Amersham-Pharmacia, Sweden). To increase reproducibility of measurements and score dot intensity the assay with internal control was developed and performed every time the sera were tested. The reproducibility of measurement was increased by using the ratio of antibody concentrations as determined by including positive and negative controls in each experiment. The negative control sera were used to determine cut-



off values for the RI of each antigen dot. The cut-off values were quantified by adding 3 times the standard deviation to the means of the readings obtained with the negative control sera.

**Standard ELISA for anti-HIV.** The antibody response to HIV was also determined by HIVAB HIV-1/HIV-2 EIA (Abbott Laboratories, USA).

**Statistical analysis.** To access reproducibility, intra-assay (one serum with strong reactivity for all HIV-1 and HIV-2 proteins in 8 replicate) and inter-assay (3 serum samples examined 8 times) analysis were performed. Mean RI of each dot and corresponding coefficient of variability (CV) were calculated. The correlation between data obtained using the standard ELISA and the DB assays was analyzed by regression ANOVA and the Pearson correlation coefficient using SPSS 13 software.

To determine the optimal DB conditions, different amounts of antigen and different dilutions of serum samples and of the conjugate were tested to obtain the highest signal-to-noise ratios for positive and negative sera. A linear relationship between DR of bands and dilutions was observed ( $r=0.869$ ;  $p=0.05$ ). A strong correlation was found between the results obtained with the DB assay and standard ELISA. To further evaluate the reproducibility of quantitation of HIV antibodies, the RI obtained from the same antigen were compared in intra- and inter-assay tests. Intra-assay CV ranged from 2.4% for gp41 and gp120 to 3.4% for p24, while inter-assay CV ranged from 2.3% for p24 to 7.8% for gp36.

Quantitative DB assay, which were read using a video camera based densitometer connected to a personal computer for quantitative image analysis, are described.<sup>5</sup> Taking into the account that automated quantification of band intensities gives objective results, the presence of a low cut-off allowed avoiding the misclassification of dots. A statistically significant concordance was found when the results obtained and compared. This demonstrated that the quantification of antibodies against single HIV antigens by quantitative DB assays is comparable with the titers obtained using a standard ELISA.

With regard to reproducibility of the results, both intra- and inter-assay precision tests gave acceptable results. It must be noted that the inter-assay CV of the RIs in the DB was lower than 10% for all the dots. In intra-assay tests, the CV was always below 5% for each band. The results of our study demonstrated that the quantitative DB assay proved convenient for characterization of specific antibody production against single HIV antigens. Quantified DB has the advantage that specific anti-HIV antibody can be quantified, thus saving time and

labor. Furthermore, the use of a computer assisted video camera offered the advantage of a permanent storage of image data, thus allowing comparison between samples analyzed at different times, while membranes stained with chromogenic substrates can lose their color differentiation overtime. Further investigation demonstrated that the ratio of p24 and gp41 antibodies was highly predictive of the risk of developing AIDS.

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## Procalcitonin marker for sepsis diagnosis. Evaluating a rapid immunochromatographic test

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Despite aggressive antimicrobial therapy and intensive medical care, mortality for sepsis remains high and this syndrome is still the leading

cause of death in intensive care units.<sup>1</sup> Although, many factors may affect the mortality, but one important factor is the lack of reliable diagnostic assays for early identifying those patients at risk for developing severe sepsis and septic shock.<sup>2</sup> Most confirmatory microbiological test results are time-consuming and available for at least 24 hours. Procalcitonin (PCT), a precursor protein of calcitonin and katalcalcin has recently drawn attention as an early specific marker for sepsis.<sup>3</sup> It is presumed that PCT level correlates strongly with infection severity and therefore, may provide as a useful objective data for sepsis diagnosis.<sup>4,5</sup> The aim of this study is to investigate the specificity and sensitivity of a commercial semi-quantitative immunochromatographic PCT rapid test for early diagnosis of sepsis and possibly severe sepsis and septic shock.

We conducted this prospective, cross-sectional, case control survey on patients who filled the systemic inflammatory response syndrome (SIRS) criteria published by American college of chest physicians and society of critical care medicine (ACCP/SCCM-criteria) with and without infection. In this study sepsis associated with organ dysfunction, hypotension or hypo perfusion was considered severe sepsis. Sepsis with hypotension despite adequate fluid therapy accompanied by perfusion abnormalities considered as septic shock. Fifty patients (32 males and 18 females; aged 18-94 years; mean age  $56 \pm 38$  years) were admitted in Al-Zahra Hospital, Isfahan (Central Iran) during February 2004 to February 2005. Of these, 25 [19 (76%) males, 6 (24%) females] with sepsis had positive blood culture and 25 [13 (25%) males and 12 (48%) females] with SIRS had no infections. After taking 2 ml of venous blood sample from each patient at admission, serum samples were frozen at  $-20^{\circ}\text{C}$ . Samples with hemolysis were excluded. The PCT level was measured using a semi-quantitative immunochromatographic rapid test (Kits were prepared from BRAHS PCT-Q, BRAH Diagnostica, Germany). All samples were examined after bringing to room temperature, a new individual test was used for each determination, 6 drops, using the enclosed dropper pipette in the cavity of the kit, and after 30 minutes at room temperature the PCT concentration range of the sample was determined. A PCT concentration  $\geq 0.5$  ng/ml can be seen as a reddish band; the color intensity of the band is directly proportional to the PCT concentration. The validity of the test was checked in comparison of the control band. The PCT reference ranges, and interpretation were as follows: slightly elevated PCT = 0.5 ng/ml, moderately elevated  $>0.5$  ng/ml, markedly elevated PCT  $\geq 2$  ng/ml and severely elevated  $\geq 10$  ng/ml. Data were analyzed by t student-

**Table 1** - Procalcitonin (PCT) level in SIRS patients without infection and sepsis group.

Group	n (%)	PCT level (ng/ml)				
		0	0.5	$>0.5$	$\geq 2$	$\geq 10$
SIRS without infection	25 (50)	24	1	-	-	-
Sepsis	12 (24)	3	3	4	2	-
Sepsis syndrome	6 (12)	-	-	-	6	-
Septic shock	7 (14)	-	-	1	3	3
<b>Total</b>	<b>50 (100)</b>	<b>27</b>	<b>4</b>	<b>5</b>	<b>11</b>	<b>3</b>

SIRS - systemic inflammatory response syndrome,  
PCT - procalcitonin

test, and one way analysis of variance (ANOVA) using SPSS software version 11. Twenty-two (88%) patients with sepsis had positive PCT titer as follows: 3 with slightly elevated PCT, 5 with moderately elevated PCT, 11 with markedly elevated PCT, 3 with severely elevated PCT and 3 with zero PCT. One (4%) of SIRS group without infection had positive titer and 24 (96%) had negative titer (**Table 1**). Therefore, the test has a 95.6% positive predictive value and 88.8% negative predictive value. All patients with severe sepsis and septic shock had over moderate level of PCT, that shows PCT level is higher in progressed septic patients. Although measurement of PCT with LUMI test®, an immunoluminometric assay, has an analytical assay sensitivity of approximately 0.1 ng/ml, but this test needs luminometer that could not be available in all hospitals. This semi-quantitative rapid test can determine plasma PCT level (limit range 0.5 ng/ml) anywhere, anytime, with a simple test procedure. Massive induction of PCT synthesis indicates a severe systemic inflammation response to a systemic nonviral infection and increased risk of fatal outcome. Although, other markers IL6, IL8, C-reactive protein (CRP), serum amyloid, have been used for differentiation of SIRS and sepsis, but PCT level is more useful than other markers to discriminate between sepsis, severe sepsis and septic shock. Among cytokines studied to date, IL6 and IL8 show most consistent correlation of outcome in critically ill patients, but do not discriminate between infectious and non-infectious causes. The CRP is not specific for infection and does not correlate with severity. The PCT titer can aid in diagnosis, monitoring and outcome prediction in septic patients and helps in making decision to do empirical antibiotic therapy.

We suggest PCT can be considered as a routine and useful test in the initial work-up of sepsis patients.

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## Comparison of glycemic control of type 2 diabetes between private hospital and governmental hospital

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The development of microvascular complications in patients with type 2 diabetes mellitus can be slowed by strict glycemic control.<sup>1</sup> The efficacy of the treatment requires methods to estimate the glycemic control. The mean glucose concentrations measured before and after meals were taken as one of these methods. This has been replaced by the simpler measurement of glycosylated hemoglobin. Strict glycemic control in type 2 diabetes depends on the compliance of the patients. The compliance to the

medications depends on the education of the patients and the ability of the patients to buy the medications. Oral anti-glycemic drugs and insulin are not cheap and need to be continued forever. Treatments of diabetes in our country are given to our patients either by governmental institutions or by private hospital. Based on my 10 years working experience in both institutions, not all of our patients were insured, furthermore, not all patients admitted in government hospitals were insured. Whereas patients treated in private hospitals were either insured or in good financial status. We studied groups of patients with similar duration of type 2 diabetes, and with similar ages treated either in the governmental hospital or in the private hospital. We aim to find whether significant differences in glycemic control exist between both groups.

We carried out a retrospective study on patients with type 2 diabetes mellitus for more than 5 years, followed in a diabetic clinic for at least one year. The patients were either visiting the diabetic clinics at King Abdul-Aziz University Hospital, or the diabetic clinics at Dr. Soliman Fageeh Hospital, Jeddah, Kingdom of Saudi Arabia. To obtain good results we compared patients with similar ages, between 40-50 years. Patients not in regular follow up, and patients with diseases (such as chronic diseases and others) that prevent them from tight control were excluded from the study. A data sheet prepared for this study includes information on patient's age, gender, and duration of diabetes, blood glucose levels, and glycosylated hemoglobin. The last results of the fasting blood glucose and glycosylated hemoglobin after at least one year of follow-up was documented in the data sheets. These data sheets were filled during their visits to the out patient clinic.

Statistical analysis on the results of the blood glucose and glycosylated hemoglobin in both groups were carried out using the Statistical Package for Social Science software version 10. Mean  $\pm$  SD was determined for categorical variable and a  $p$ -value  $<0.05$  was considered significant.

Two-hundred patients in each group were included in the study. The results showed significant differences in the control of blood glucose in patients treated in private hospital (**Table 1**). The fasting blood glucose in patients treated, and followed in governmental hospital was ranging between 113-267 mg/dl compared with the patients treated in the private hospital - range between 87-183 mg/dl. The mean fasting blood glucose in patients treated in governmental hospital was 189.7 mg/dl compared with 111.3 mg/dl in patients treated in private hospital ( $p=0.001$ ). The last glycosylated hemoglobin carried out for the patients followed in



## Comparison of glycemic control

**Table 1** - Clinical and laboratory findings in both groups.

Items	Patients treated in governmental hospital	Patients treated in private hospital	Statistical finding
Age [mean (year)]	46.3	46.1	Not significant.
Male	93	111	Not indicated
Female	107	81	Not indicated
Systolic pressure	141	133	$p = 0.001$
Diastolic pressure	90	88	$p = 0.013$
LDL	141.3	107	$p = 0.001$
HDL	29	31	$p = 0.017$
TG	189	153	$p = 0.001$
FBG	189.7	111.3	$p = 0.001$
HbA1c	9.89%	7.1%	$p = 0.001$

LDL-low-density lipoprotein, HDL - high-density lipoprotein, TG - triglyceride, FBG- fasting blood glucose, HbA1c - glycosylated hemoglobin

the governmental hospital were ranged between 6.7-18.9% (mean 9.89%) where in patients followed in the private hospital were between 6.1-10.2% (mean 7.1%). The  $p$ -value between the 2 groups of patients was very significant ( $p=0.001$ ). For the numbers of patients who achieved the glycemic goals of treatment (HbA1c <7%), there were only 23 patients treated in the governmental hospital compared with 117 patients treated in the private hospital ( $p=0.001$ ).

Thirty-seven patients treated in the governmental hospital received sulfonylureas alone, and 133 patients received metformin in combination with sulfonylureas. The remaining 30 patients out of the 200 patients followed in the governmental hospital were either treated completely with twice a day insulin or combined insulin with oral antiglycemic drugs. For the patients followed in private hospitals, they were treated more with insulin. Eighty-seven patients were treated with insulin. Mixed insulin was taken by 47 patients either twice a day or 3 times a day. Long acting insulin (glargine) was added to oral anti-glycemic drugs in 40 patients. One-hundred thirteen patients was treated with oral anti-glycemic drugs alone. Combined thiazolidendion, metformin and sulfonylureas were the treatments in 37 patients. Sulfonylureas and metformin only were the treatment received in 57 patients, where 19 patients were treated by sulfonylureas alone.

Good glycemic control in patients who suffered from type 2 diabetes requires more than one oral antiglycemic drug. Treatment should start either with sulfonylureas or metformin, depending on the patients body weight. Combination of both drugs were required if blood glucose were not well controlled. Thiazolidendion or long acting insulin was added if needed.

Patients in private hospital are either insured or have a good financial status and are able to buy

the prescribed drugs. government hospitals on the other hand, are not dispensing the medications freely and most of the patients cannot afford to buy the medicine.

The goal of our treatment must prevent or delay chronic complications and this can be achieved if the normal fasting blood glucose and glycosylated hemoglobin is be less than 7%. Glycosylated hemoglobin reflects the mean glucose concentration over the previous 6-8 weeks. A strong correlation was noted, such that a HbA1c of 7% represented as mean blood glucose value of approximately 150 mg/dl, and a HbA1c value of 9% represented a mean blood glucose value of approximately 210/dl.<sup>2</sup> The HbA1c assays were carried out by different methods. For instance, some assays separate glycated hemoglobin from non glycated based on charge differences using ion exchange chromatography or electrophoresis. Other assays use affinity chromatography to separate glycated from a non glycated hemoglobin, bases on structural characteristics. Fasting blood glucose correlates fairly well with the HbA1c value and can be used with the HbA1c to estimate glycemic control. Immediate patient feedback at physician visit regarding HbA1c values may improve glycemic control.<sup>3,4</sup> The factors that contribute to the worsening of glycemic control are decrease compliance to diet or exercise or the medical regimen or weight gain or intercurrent illness.<sup>5</sup> The progression of the underlying disease process, and the patients may have type 1 diabetes with gradual destruction of the pancreatic B-cells were important factors in treatment failure.

The patients treated and followed in the governmental hospital revealed poor glycemic control due to poor compliance to the medications. Systolic blood pressure and low density lipoprotein were controlled better in patients treated in private hospital. This may be related to the inability of the patients

treated in government hospitals to continue the medication due to the expenses. Whereas in patients treated in the private hospital revealed good glycemic control with good compliance to the medications.

In conclusion, I recommend that dispensing of medication for diabetics should be free to all patients and that the study showed the importance of medical insurance to all patients.

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